

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 June 2006 (15.06.2006)

PCT

(10) International Publication Number  
**WO 2006/061364 A1**

(51) International Patent Classification:  
C07D 209/88 (2006.01) A61P 9/04 (2006.01)  
A61K 31/403 (2006.01) A61P 9/12 (2006.01)

(74) Agent: LONGONI, Alessandra; Zambon Group S.P.A.,  
Intellectual Property Dept., Via Lillo del Duca, 10, I-20091  
Bresso (IT).

(21) International Application Number:  
PCT/EP2005/056469

(81) Designated States (*unless otherwise indicated, for every  
kind of national protection available*): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,  
LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI,  
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,  
SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US,  
UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:  
5 December 2005 (05.12.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
04106438.7 9 December 2004 (09.12.2004) EP

(84) Designated States (*unless otherwise indicated, for every  
kind of regional protection available*): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,  
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,  
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): ZAM-  
BON GROUP S.P.A. [IT/IT]; Via della Chimica, 9,  
I-36100 Vicenza (IT).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): TREPAT GUIXER,  
Elisenda [ES/ES]; Zambon SA, Maresme 5 Poligono Ur-  
vasa, E-08130 Sta Perpetua de Mogoda (ES). MUNOZ  
ALVAREZ, Anna [ES/ES]; Zambon SA, Maresme 5  
Poligono Urvasa, E-08130 Sta Perpetua de Mogoda (ES).  
POMARES MARCO, Marta [ES/ES]; Zambon SA,  
Maresme 5 Poligono Urvasa, E-08130 Sta Perpetua de  
Mogoda (ES). MARQUILLAS OLONDRIZ, Francisco  
[ES/ES]; Zambon SA, Maresme 5 Poligono Urvasa,  
E-08130 Sta Perpetua de Mogoda (ES).

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: PROCESS FOR THE PREPARATION OF CARVEDILOL AND ITS ENANTIOMERS

(57) Abstract: The present invention relates to a process for the preparation of carvedilol as well as of the optically active R and S enantiomers thereof and of mixtures of these enantiomers and, more particularly, relates to an improved process for the preparation of carvedilol and its enantiomers characterized by the use of ethyl acetate as reaction solvent.

WO 2006/061364 A1

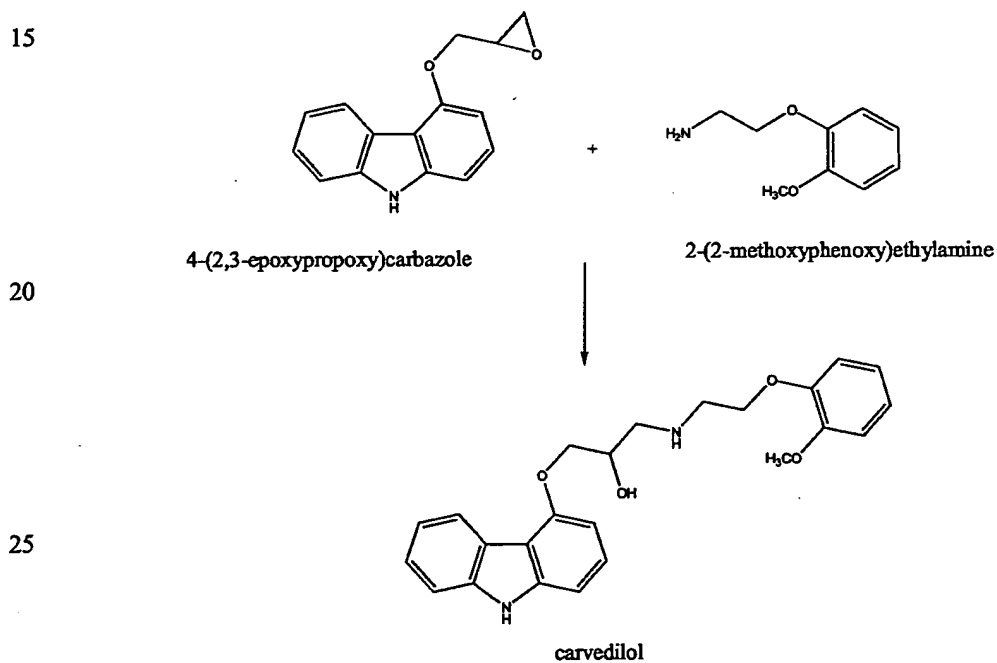
# "PROCESS FOR THE PREPARATION OF CARVEDILOL AND ITS ENANTIOMERS"

\*\*\*\*\*

The present invention relates to a process for the preparation of carvedilol as well as of the  
5 optically active R and S enantiomers thereof and of mixtures of these enantiomers and, more particularly, relates to an improved process for the preparation of carvedilol and its enantiomers characterized by the use of ethyl acetate as reaction solvent.

Carvedilol, ( $\pm$ )-1-(carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol, is a nonselective  $\beta$ -adrenergic blocker with  $\alpha_1$ -blocking activity. Carvedilol is the active  
10 ingredient of COREG<sup>®</sup> and it is indicated for the treatment of congestive heart failure and for the management of hypertension.

Carvedilol was first described in US 4,503,067 (Boehringer Mannheim GmbH) and the preparation described therein corresponds to the following reaction scheme:



For an easier reference, intermediates 4-(2,3-epoxypropoxy)carbazole and 2-(2-methoxyphenoxy)ethylamine will be indicated herein after also as EPOC and MFA,  
30 respectively.

- 2 -

According to US 4,503,067, the reaction between EPOC and MFA is preferably carried out in a solvent which is inert under reaction conditions, for example toluene, dioxan, ethylene glycol dimethyl ether, isopropanol or dimethylformamide.

- 5 In example 2 of US 4,503,067, carvedilol is prepared by reaction of EPOC with MFA in ethylene glycol dimethyl ether as reaction solvent. Crude carvedilol is then triturated with diethylether and recrystallized from ethyl acetate to give pure carvedilol form II (m.p. 114°C-115°C).

- As described in US 4,697,022, the preparation of carvedilol enantiomers follows the same  
10 reaction scheme. In examples 7 and 8 of US 4,697,022, (R) and (S)-carvedilol are prepared from the respective EPOC enantiomers by reaction with MFA in isopropanol.

The process for the preparation of carvedilol or its enantiomers described in US 4,503,067 and US 4,697,022 have some drawbacks, mainly due to the formation of a bis-impurity deriving from the reaction of 2 molar equivalents of EPOC with 1 molar equivalent of MFA.

- 15 These drawbacks can be overcome either by using a high excess (higher than 2.8) of MFA, as described in WO02/00216 (Teva Pharmaceutical Industries) or by using a benzyl derivative of MFA (benzyl-MFA), as described in EP 0 918 055 (Egis Gyogyszergyar).

- Both alternative methods, however, are not industrially advantageous since they require the use of a high amount of reactants (MFA), which remains unreacted and should be recovered  
20 from the reaction mixture, or the addition of a further step (debenzylation) in the process.

We have now found an improved process for the preparation of carvedilol which does not show the drawbacks of the already known processes and allows to prepare carvedilol or its enantiomers in good yields and with high purity.

- Therefore, object of the present invention is a process for the preparation of carvedilol or its  
25 enantiomers by reaction of EPOC or its enantiomers with an excess of MFA characterized by the fact that the reaction solvent is ethyl acetate.

- The improved process object of the present invention has the advantage of requiring no additional step in the synthesis, no high excess of MFA and, moreover, it allows to carry out the overall process by using the same solvent, ethyl acetate, that is the same solvent used  
30 also for the final purification/crystallization of the product.

- 3 -

The man skilled in the art can easily acknowledge that the same advantages can derive from the use of other acetic acid esters, such as isopropyl acetate and the like, as a reaction solvent. Exclusively for practical reasons, ethyl acetate is the preferred solvent in the process object of the present invention.

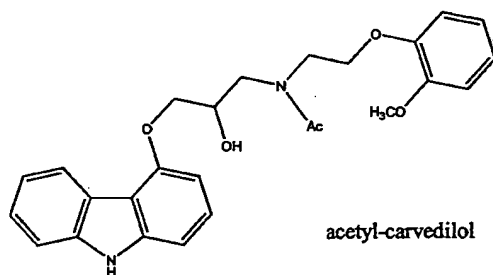
It is evident to the man skilled in the art the advantage deriving from the use of the same solvent in the overall process. However, the replacement of the reaction solvents described in the literature with ethyl acetate is a solution to the problem of the prior art processes which cannot be derived from the prior art teaching.

10 In fact, US 4,503,067 and US 4,697,022 describe several solvents useful for the reaction of EPOC or its enantiomers with MFA but all these solvents must be inert under reaction conditions. Ethyl acetate is an ester and, as any carbonyl derivative, it cannot be considered an inert solvent in the presence of amines as reactants (for a general reference see Jerry March – Advanced Organic Chemistry – Third Edition, 1985, John Wiley & Sons –page

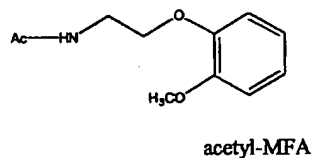
15 375 ).

Indeed, in the process object of the present invention some impurities deriving from the use of ethyl acetate can be detected in the reaction mixture as well as in crude carvedilol. These impurities are mainly acetyl-carvedilol and acetyl-MFA of formula

20



25



30

- 4 -

However, the amount of these impurities in the reaction mixture is always lower than 0.5% and they can be easily removed from the final product by crystallization in ethyl acetate according to known methods.

- 5 Moreover, ethyl acetate is specifically mentioned to be a useless solvent in this kind of reaction. See in particular EP 0 918 055 which describes that by replacing ethylene glycol dimethyl ether with ethyl acetate in the reaction between EPOC and benzyl-MFA, practically no reaction occurs.

In the process object of the present invention an excess of MFA over EPOC or its enantiomers is used. Preferably the molar excess is from 1.5:1 to 2.5:1, most preferably from 1.8:1 to 2.2:1. Still more preferred molar ratio MFA:EPOC is 2:1.

The reaction between EPOC or its enantiomers and MFA is carried out under heating.

The reaction temperature is preferably from 50°C to the reflux temperature of the reaction mixture. More preferably the reaction is carried out under reflux (about 78°C).

- 15 Generally, the reaction takes some hours to be completed depending on the reaction temperature.

The process object of the present invention is preferably used for the preparation of carvedilol, more preferably for the preparation of carvedilol form II.

- Crude carvedilol or crude carvedilol enantiomers are separated from the reaction mixture by cooling at 0°C±5°C after filtration of the activated carbon eventually added to the reaction mixture.

The resultant crude wet carvedilol or carvedilol enantiomer is then purified by crystallization in ethyl acetate according to known methods.

Carvedilol and its enantiomers are obtained with high yields and high purity.

- 25 Carvedilol and carvedilol enantiomers obtained with the process object of the present invention are characterized by a low content of residual solvent, in particular by a low content (less than 500 ppm) of ethyl acetate as the only residual solvent.

Therefore, object of the present invention is carvedilol, (R)-carvedilol, (S)-carvedilol or mixture thereof containing less than 500 ppm of ethyl acetate as the only residual solvent.

- 30 Preferred object of the present invention is carvedilol form II containing less than 500 ppm

- 5 -

of ethyl acetate as the only residual solvent.

Carvedilol and carvedilol enantiomers obtained with the process object of the present invention are particularly suitable for the pharmaceutical use.

- 5 Therefore, pharmaceutical compositions containing a therapeutically effective amount of carvedilol or an enantiomer thereof prepared according the process of the present invention in admixture with a suitable pharmaceutically acceptable carrier are a further object of the present invention.

Preferred pharmaceutical compositions according to the present invention are tablets, still  
10 more preferred are tablets containing carvedilol.

Particularly preferred pharmaceutical compositions are tablets containing carvedilol form II. The pharmaceutical compositions according to the present invention contains conventional pharmaceutically acceptable carrier and can be prepared according to conventional method.

A practical embodiment of the process object of the present invention is the following.

- 15 Ethyl acetate, activated carbon, EPOC and a molar excess of MFA are added into a reactor and the resultant mixture is heated under reflux temperature for about 6 hours.

Then, the activated carbon is filtered off and the resultant solution is cooled to room temperature and then to about 0+5°C and kept under stirring.

The crystals are separated by centrifugation and washed with ethyl acetate.

- 20 The resultant crude wet carvedilol is dissolved in ethyl acetate by heating under reflux. After cooling, separation by centrifugation and drying, pure carvedilol form II is obtained. For better illustrating the invention the following examples are given.

#### Example 1

About 4 parts of ethyl acetate were charged into a reactor, under stirring. About 1.4 parts of

- 25 MFA, about 0.045 parts of activated carbon and about 1 part of EPOC were added.

The mixture was heated to the reflux temperature of ethyl acetate (about 78°C).

The reaction mixture was stirred at about 78°C for about six hours.

The progress of the reaction was checked by TLC.

When the reaction was completed, the mixture was filtered at a temperature not below 65°C

- 30 in order to separate the activate carbon.

- 6 -

The mixture was cooled to room temperature and then to about  $0 \pm -5^{\circ}\text{C}$  and stirred for about 1 hour.

5 The resultant crystals were separated by centrifugation and washed with about 1 part of ethyl acetate.

The resultant wet crude carvedilol was charged into a stainless steel reactor and about 6 parts of ethyl acetate and 0.045 parts of activated carbon were added.

10 The mixture was heated to the reflux temperature of ethyl acetate (about  $78^{\circ}\text{C}$ ), until the dissolution of the crystals. The mixture was stirred at about  $78^{\circ}\text{C}$  for about 1 hour and then filtered at a temperature not below  $65^{\circ}\text{C}$  in order to separate the activate carbon.

The mixture was allowed to cool at about  $20^{\circ}\text{C}$  and then to about  $0 \pm -5^{\circ}\text{C}$  and stirred for about 1 hour.

The resultant crystals were separated by centrifugation and washed with about 1 part of ethyl acetate.

15 The wet crystallized carvedilol was charged into a stainless steel reactor and about 4 parts of ethyl acetate were added.

The mixture was heated to the reflux temperature of ethyl acetate (about  $78^{\circ}\text{C}$ ), until dissolution of the crystals.

20 The mixture was stirred at about  $78^{\circ}\text{C}$  for about 1 hour and filtered at a temperature not below  $65^{\circ}\text{C}$ .

The mixture was allowed to cool at about  $20^{\circ}\text{C}$  and then to about  $0 \pm -5^{\circ}\text{C}$  and stirred for about 1 hour.

The resultant crystals were separated by centrifugation and washed with about 1 part of ethyl acetate.

25 The wet product was dried in an air dryer at  $50^{\circ}\text{C}$  until the residual solvent ethyl acetate was within the specifications.

Yield: about 1.05 to 1.10 parts of pure carvedilol for 1 part of EPOC.

#### Example 2

30 By repeating the procedure as described in example 1 but carrying out the reaction at a temperature of  $70^{\circ}\text{C}$ ,  $60^{\circ}\text{C}$  and  $50^{\circ}\text{C}$ , substantially the same results were obtained with a

- 7 -

prolonged reaction time of 8 hours, 10 hours and 16.5 hours, respectively.

#### Example 3

The procedure as described in example 1 was repeated obtaining substantially similar results  
5 by using a molar ratio EPOC:MFA of 1:1.5, 1:1.7, 1:1.8 and 1:2.2.



- 8 -

Claims

- 1) A process for the preparation of carvedilol or its enantiomers by reaction of 4-(2,3-epoxypropoxy)carbazole or its enantiomers with an excess of 2-(2-methoxyphenoxy)ethylamine characterized by the fact that the reaction solvent is ethyl acetate.  
5
- 2) A process according to claim 1 wherein 2-(2-methoxyphenoxy)ethylamine is used in molar excess from 1.5:1 to 2.5:1.
- 3) A process according to claim 2 wherein the molar excess is from 1.8:1 to 2.2:1.
- 10 4) A process according to claim 3 wherein the molar excess is 2:1.
- 5) A process according to claim 1 for the preparation of carvedilol form II.
- 6) Carvedilol, (R)-carvedilol, (S)-carvedilol or mixture thereof containing less than 500 ppm of ethyl acetate as the only residual solvent.
- 7) Carvedilol form II containing less than 500 ppm of ethyl acetate as the only residual  
15 solvent.
- 8) Pharmaceutical compositions containing a therapeutically effective amount of carvedilol, (R)-carvedilol, (S)-carvedilol or mixture thereof, containing less than 500 ppm of ethyl acetate as the only residual solvent, in admixture with a suitable pharmaceutically acceptable carrier.
- 20 9) Pharmaceutical compositions containing a therapeutically effective amount of carvedilol form II, containing less than 500 ppm of ethyl acetate as the only residual solvent, in admixture with a suitable pharmaceutically acceptable carrier.
- 10) A process for the preparation of carvedilol or its enantiomers by reaction of 4-(2,3-epoxypropoxy)carbazole or its enantiomers with an excess of 2-(2-methoxyphenoxy)ethylamine characterized by the fact that the reaction solvent is an acetic  
25 acid ester.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2005/056469

## A. CLASSIFICATION OF SUBJECT MATTER

C07D209/88 A61K31/403 A61P9/04 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 503 067 A (WIEDEMANN ET AL) 5 March 1985 (1985-03-05) cited in the application Example 2 (columns 5-6). Lines 31-35 (column 3). Claim 12.	6-9
A		1,10
X	US 4 697 022 A (LEINERT ET AL) 29 September 1987 (1987-09-29) cited in the application Examples 7-8 (columns 8-9). Lines 9-13 (column 1).	6,8
A		1,7,9,10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*A\* document member of the same patent family

Date of the actual completion of the international search

20 March 2006

Date of mailing of the international search report

07/04/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Menchaca, R

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2005/056469

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4503067	A	05-03-1985	AT 375639 B	27-08-1984
			AT 276279 A	15-01-1984
			AU 522975 B2	08-07-1982
			AU 4582079 A	18-10-1979
			BG 61419 B2	31-07-1997
			CA 1129416 A1	10-08-1982
			CS 227007 B2	16-04-1984
			CS 9104200 A3	15-04-1992
			DD 143607 A5	03-09-1980
			DE 2815926 A1	18-10-1979
			DK 141979 A	14-10-1979
			EP 0004920 A1	31-10-1979
			ES 479396 A1	16-04-1980
			FI 791142 A	14-10-1979
			HK 2385 A	18-01-1985
			HU 179433 B	28-10-1982
			IL 57020 A	30-07-1982
			JP 1023462 B	02-05-1989
			JP 1545837 C	28-02-1990
			JP 54157558 A	12-12-1979
			JP 63258416 A	25-10-1988
			LT 2628 R3	25-04-1994
			LU 88320 A9	04-05-1994
			MX 9203380 A1	01-09-1992
			NL 930110 I1	18-10-1993
			SG 52284 G	29-03-1985
			SU 810079 A3	28-02-1981
			ZA 7901732 A	28-05-1980
US 4697022	A	29-09-1987	AU 551116 B2	17-04-1986
			AU 2848084 A	29-11-1984
			CA 1259071 A1	05-09-1989
			DE 3319027 A1	29-11-1984
			DK 91393 A	06-08-1993
			DK 255184 A	27-11-1984
			EP 0127099 A1	05-12-1984
			ES 8502683 A1	16-04-1985
			FI 842046 A	27-11-1984
			GR 81577 A1	11-12-1984
			HU 34160 A2	28-02-1985
			IE 57533 B1	24-03-1993
			IL 71876 A	30-10-1987
			JP 1818634 C	27-01-1994
			JP 5027622 B	21-04-1993
			JP 59222473 A	14-12-1984
			JP 1917129 C	23-03-1995
			JP 5208957 A	20-08-1993
			JP 6013508 B	23-02-1994
			KR 8601761 B1	21-10-1986
			NO 842084 A	27-11-1984
			NZ 208254 A	29-11-1988
			PH 22749 A	28-11-1988
			PT 78633 A	01-06-1984
			US 4824963 A	25-04-1989
			US 4985454 A	15-01-1991
			US 5071868 A	10-12-1991
			ZA 8403976 A	30-01-1985